

AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. (Currently amended) A genotyping method comprising
using hybridizing a target nucleic acid to a DNA chip on which an optimal probe pair is
immobilized,
wherein the optimal probe pair consists of a wild type-perfect match probe for a mutation
site on the target nucleic acid and a mutant type-perfect match probe are immobilized for each the
mutation site,-
wherein the optimal probe pair is selected by:
designing a plurality of probe pairs for the mutation site, wherein a probe pair consists of
a wild type-perfect match probe and a mutant type-perfect match probe;
immobilizing the plurality of probe pairs on a substrate to manufacture an optimal probe
pair screening chip;
hybridizing a standard nucleic acid to the optimal probe pair screening chip;
collecting quantitative hybridization intensity data;
calculating a value for each probe pair of the following equation:
$$\frac{\{Mean(\ln(r^{wt})) - 2 SD(\ln(r^{wt}))/\sqrt{N^{wt}}\} - \{Mean(\ln(r^{mt})) + 2SD(\ln(r^{mt}))/\sqrt{N^{mt}}\}}{N}$$

wherein N denotes a number of times hybridization of the standard nucleic acid has been
performed;
 r^{wt} is a ratio between a hybridization intensity of a wild type standard nucleic acid to the
wild type-perfect match probe and a hybridization intensity of the wild type standard nucleic acid
to the mutant type-perfect match probe;
 r^{mt} is a ratio between a hybridization intensity of a mutant type standard nucleic acid to
the wild type-perfect match probe and a hybridization intensity of the mutant type standard
nucleic acid to the mutant type-perfect match probe; and
 $Mean$ and SD denote a mean value and a standard deviation, respectively, of $N \ln(r)$
values, which are obtained by hybridizing the standard nucleic acid to the DNA chip N times; and
selecting the probe pair having the largest value as the optimal probe pair.

2. (Currently amended) The genotyping method of claim 1, wherein at least two optimal probe pairs for the mutation site are immobilized ~~for each mutation site of~~ on the DNA chip.

3. (Currently amended) The genotyping method of claim 2, wherein at least two wild type-perfect match probes for the mutation site are arranged side by side and at least two mutant type-perfect match probes for the mutation site are arranged side by side adjacent to the wild type-perfect match probes ~~for each mutation site of~~ on the DNA chip.

4. (Cancelled)

5. (Currently amended) The genotyping method of claim 1, further comprising:

(a) setting up a genotyping algorithm ~~using data obtained from~~ for hybridization of an ~~identified~~ a standard nucleic acid to the DNA chip; and

(b) genotyping ~~an unknown~~ the target nucleic acid by substituting an input vector that ~~are~~ is calculated from hybridization of the target nucleic acid to the DNA chip into the genotyping algorithm.

6. (Currently amended) The genotyping method of claim 5, wherein (a) comprises:

(a-1) collecting quantitative hybridization intensity data obtained from hybridization of the ~~identified~~ standard nucleic acid to the DNA chip;

(a-2) ~~calculating the a ratio, r_{ij} , for every pairing of a wild type-perfect match probe (wp_i) of an optimal probe pair (i) immobilized on the DNA chip for the mutation site on the target nucleic acid and a mutant type-perfect match probe (mp_j) of an optimal probe pair (j) immobilized on the DNA chip for the mutation site on the target nucleic acid,~~

wherein the ratio, r_{ij} , is between the a hybridization intensity of the standard nucleic acid to the wild type-perfect match probe (wp_i) and the a hybridization intensity of the standard nucleic acid to the mutant type-perfect match probe (mp_j) for every probe pair,

~~selecting the a Hodge-Lehman median from among the calculated ratios using Hodge-lehman estimation, and~~

~~taking the natural logarithm of the median as a ratio component of a vector used to set up the genotyping algorithm for the DNA chip; and~~

(a-3) repeating (a-1) and (a-2) with a plurality of DNA chips to obtain ratio components for a set of vectors ~~and setting up the genotyping algorithm using the set of vectors.~~

7. (Currently amended) The genotyping method of claim 6, wherein (a-3) further comprises calculating logistic regression coefficients for the ~~genotyping algorithm using the set of~~ vectors.

8. (Currently Amended) The genotyping method of claim 6, wherein (a-2) further comprises

obtaining a product, a_{ij} , for every pairing of a wild type-perfect match probe (wp_i) of an optimal probe pair (i) immobilized on the DNA chip for the mutation site on the target nucleic acid and a mutant type-perfect match probe (mp_j) of an optimal probe pair (j) immobilized on the DNA chip for the mutation site on the target nucleic acid,

wherein the product, a_{ij} , is obtained by multiplying the hybridization intensities-intensity of each probe pairthe standard nucleic acid to the wild type-perfect match probe (wp_i) and the hybridization intensity of the standard nucleic acid to the mutant type-perfect match probe (mp_j),

selecting the Hodge-Lehman median from among the products-using Hodge-lehman estimation,

dividing the natural-logarithm of the median by two to obtain an intensity component of the vector for the DNA chip-used to set up the genotyping algorithm;

wherein the genotyping method further comprises

plotting a graph with the Y-axis parameterized by the ratio component and the X-axis parameterized by the intensity component before (a-3); and

the genotyping algorithm comprises logistic regression coefficients is set up in (a-3) using of all of the ratio components if the ratio components -of the graph has a independence-onare independent of the intensity components or comprises logistic regression coefficients using of only some-the ratio components which are independent of the intensity components if the ratio components of the graph has a dependence-are dependent on the intensity components.

9. (Currently Amended) The genotyping method of claim 6, wherein (a-2) further comprises

~~taking the larger of~~ comparing, for every pairing of a wild type-perfect match probe (w_{pi}) of an optimal probe pair (i) immobilized on the DNA chip for the mutation site on the target nucleic acid and a mutant type-perfect match probe (m_{pi}) of an optimal probe pair (j) immobilized on the DNA chip for the mutation site on the target nucleic acid, the hybridization intensities ~~intensity of each probe pair~~ the standard nucleic acid to the wild type-perfect match probe (w_{pi}) and the hybridization intensity of the standard nucleic acid to the mutant type-perfect match probe (m_{pi}), to determine which is the larger,

~~selecting the Hodge-Lehman median from among the selected-larger hybridization intensities using Hodge-lehman estimation,~~

~~taking the natural-logarithm of the median as an intensity component of a~~ the vector for the DNA chip ~~used to set up the genotyping algorithm;~~

the genotyping method further comprises

plotting a graph with the Y-axis parameterized by the ratio component and the X-axis parameterized by the intensity component before (a-3); and

the genotyping algorithm comprises logistic regression coefficients of ~~is set up in (a-3)~~ using all of the ratio components if the ratio components of the graph has a independence on are independent of the intensity components or comprises logistic regression coefficients of using only some ~~the~~ ratio components which are independent of the intensity components if the ratio components of the graph has a dependence are dependent on the intensity components.

10. (Currently amended) The genotyping method of claim 6, further comprising filtering out quantitative hybridization intensity data obtained from bad spots from the quantitative hybridization intensity data collected in step (a-1) before (a-2),

wherein a bad spot on the DNA chip that have ~~has~~ a larger diameter than an effective spot diameter from the quantitative hybridization intensity data collected in step (a-1) before (a-2).

11. (Currently amended) The genotyping method of claim 5, wherein (b) comprises:

(b-1) collecting quantitative hybridization data obtained from hybridization of the ~~unknown~~-target nucleic acid to the DNA chip;

(b-2) calculating ~~the a~~ ratio, r_{ij} , for every pairing of a wild type-perfect match probe (wp_i) of an optimal probe pair (i) immobilized on the DNA chip for the mutation site on the target nucleic acid and a mutant type-perfect match probe (mp_j) of an optimal probe pair (j) immobilized on the DNA chip for the mutation site on the target nucleic acid,

wherein the ratio, r_{ij} , is between the a hybridization intensity of the target nucleic acid to the wild type-perfect match probe (wp_i) and the a hybridization intensity of the target nucleic acid to the mutant type-perfect match probe (mp_j) for every probe pair,

selecting the Hodge-Lehman median from among the calculated ratios ~~using Hodge-lehman~~ estimation, and

taking the ~~natural~~-logarithm of the median as an input vector for genotyping; and

(b-3) substituting the input vector into the genotyping algorithm to genotype the target nucleic acid.

12. (Currently Amended) The genotyping method of claim 11, wherein (b-3) comprises

calculating ~~the a posterior probabilities~~ probability that the target nucleic acid is a wild type ~~and a posterior probability that the target nucleic acid is~~ or a mutant type by substituting the input vector into the genotyping algorithm and

determining the genotype of the target nucleic acid to be a wild type if the posterior probability that the target nucleic acid is a wild type is greater than the posterior probability that the target nucleic acid is a mutant type or determining the genotype of the target nucleic acid to be a mutant type if the posterior probability that the target nucleic acid is a wild type is less than the posterior probability that the target nucleic acid is a mutant ~~depending on the greater posterior probability.~~

13. (Currently Amended) The genotyping method of claim ~~11~~12, wherein (b-3) further comprises:

~~calculating the posterior probabilities that the target nucleic acid is wild type or a mutant type by substituting the input vector into the genotyping algorithm to determine the genotype of the target nucleic acid to be a wild type or a mutant type depending on the greater posterior probability; and~~

~~validating the genotype determination based on a reliability requirement, wherein the reliability requirement is that of the greater posterior probability of the determined genotype be at a predetermined significance level and~~

~~deferring genotyping determination of a genotype of the target nucleic acid if the reliability requirement is not satisfied.~~

14. (Currently Amended) The genotyping method of claim 11, further comprising filtering out quantitative hybridization intensity data obtained from bad spots from the quantitative hybridization intensity data collected in step (b-1) before (b-3).

wherein a bad spot on the DNA chip has~~that have~~ a larger diameter than an effective spot diameter ~~from the quantitative hybridization intensity data collected in step (b-1) before (b-3).~~

15. (Currently Amended) The genotyping method of claim 5, further comprising correcting the genotyped results from step (b) ~~based on cross hybridization data of the probe pair for each mutation site.~~

16. (Withdrawn) A DNA chip used for a genotyping method, comprising an optimal probe pair of a wild type-perfect match probe and a mutant type-perfect match probe which are immobilized for each mutation site.